THE REMARKS

The Amendment

Applicants have amended the claims to delete the mutation in a conserved arginine. The claims as amended, are directed to a mutation in a conserved histidine.

Claim 5 is amended to correct a typographical error. SEQ ID NO: 3 is nucleotide sequence of Bac31A8. Support for the amendment can be found, for example, at page 35, line 9.

No new matter is added in the amendments. The Examiner is requested to enter the amendments.

First Restriction

In response to the first restriction requirement, Applicants are electing Group I, Claims 1-12 and 14, drawn to polypeptides, without traverse.

Further Restriction

In response to the further restriction requirement, Applicants are making the following provisional election with traverse.

Claim 4: Applicant elects naturally occurring proteorhodopsin variant of SEQ ID NO: 3 (Bac31A8).

Claim 14: Applicant elects proteorhodopsin mutant of SEQ ID NO: 165 (Bac31A8 H75N)

Claims 1, 4, 5, 7-9, and 14 read on the elected invention.

Applicants respectfully traversed the further restriction within Group I for the following reasons.

1. Unity of Invention

MPEP 809.03 states that where an application includes two or more otherwise properly divisible inventions that are linked by a claim which, if allowable, would prevent restriction. The restriction requirement is subject to the non-allowance of the linking claim. Upon the indication of allowability of the linking claim, the restriction requirement as to the linked inventions shall

be withdrawn and any claim(s) depending from or otherwise requiring all the limitations of the allowable linking claim(s) will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104

Applicants have amended the claims to cancel the claims directed to mutation in a conserved arginine. The claims as amended, are directed to mutation in a conserved histidine. **Claim 1 is the linking claim of all the remaining pending claims.** The invention of Group I is linked by the special technical features that each proteorhodopsin mutant comprises a mutation in a conserved histidine residue of a wild-type proteorhodopsin variant, and the proteorhodopsin mutant has lower pK_{th} in comparison with the wild-type proteorhodopsin variant. Such technical feature (mutation on a conserved histidine) distinguishes from any prior art.

Naturally occurring proteorhodopsin variants are highly conserved (see the amino acid alignment in Figures 3-1 to 3-8). The technical feature of mutation on a conserved histidine is patentable and is applicable to any naturally occurring proteorhodopsin variants, and is not limited to one or two proteorhodopsin variants.

Therefore, Applicants request that the restriction requirement within Group I be subject to the non-allowance of Claim 1.

2. There should not be a restriction requirement among SEQ ID NOs: 1 to 161.

MPEP 803.02 states that if the members of the Markush group are sufficiently few in number OR so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they may be directed to independent and distinct inventions.

In Claim 4, SEQ ID NOs: 1 to 161 are naturally occurring proteorhodopsin variants. They are closely related and are highly conserved as shown in the sequence alignment in Figures 3-1 to 3-8. Unless the Examiner finds prior art against the linking claim, it is unreasonable to force Applicants to elect one variant over another as the concept is the same. Therefore, Applicants request the Examiner examine them together.

3. There should not be a restriction requirement among SEQ ID NO: 164 to 178.

In Claim 15, SEQ ID NOs: 164 to 178 are proteorhodopsin mutants all having a mutation in a conserved histidine of a naturally occurring proteorhodopsin variant. These mutants are sufficiently few in number and they are so closely related that Applicants request the Examiner examine them together.

Bac31A8 H75K (SEQ ID NO: 163), Bac31A8 H75N (SEQ ID NO: 165), Bac31A8 H75Q (SEQ ID NO: 167) only differ by one amino acid on the mutation site. It is unreasonable to force Applicants to elect one over another.

4. Special Technical Feature of the Invention

A skilled person in the art would find the special technical feature that links the Group I invention throughout the application, and will conclude that the pending claims as amended, are linked together.

At page 18, lines 7-11, the specification describes:

Conserved amino acid residues that are involved in the relay of protons through the all-trans-retinal binding site, but are not in direct contact with the all-trans-retinal cofactor, are likely to affect the pH dependent spectral shift and the pKrh value of proteorhodopsin, and allow for a continued pumping of protons and therefore a productive photocycle. Applicants have identified such conserved amino acid residues in proteorhodopsins.

At page 18, lines 24-25, the specification describes:

A conserved amino acid residue of proteorhodopsin is an amino acid that is found in the equivalent position of the 81 proteorhodopsins as depicted in FIGURE 3..... FIGURE 3 shows the alignment of amino acid sequences of 81 natural proteorhodopsin variants. Examples of conserved amino acid residues (H75, R94, D227 of BAC31A8) are shown in FIGURE 3. Such conserved amino acid residues can affect the conformation of the protein and the positioning of the all-trans-retinal molecule in relation to the proteorhodopsin protein.

At page 19, lines 8-10, the specification describes:

Proteorhodopsin mutants, which have the conserved histidine substituted with an amino acid capable of forming a hydrogen bond, have an altered photochemical property that shifts the pKrh to a lower pH (more acidic) value than the wild-type proteorhodopsin.

At page 19, lines 18-24, the specification describes:

Amino acids capable of forming a hydrogen bond and suitable for substituting histidine in this invention include asparagine, glutamine, lysine, arginine, serine, theonine, tyrosine, aspartic acid (in its protonated state at acid pH), glutamic acid (in its protonated state at acidic pH), tryptophan, and any synthetic amino acid that has a functional group that is able to contribute a hydrogen to form a hydrogen bond. Preferred proteorhopsin mutants have the conserved histidine residue substituted with glutamine (Q), asparagine (N), glutamic acid (E), lysine (K), aspartic acid (D), and tryptophan (W).

At page 16, lines 10-25, the specification describes the nucleotide and amino acid sequences of 81 natural proteorhodopsin variants (Figure 1-1 to 1-81), and how they can be used to prepare mutants for this invention.

At page 20, lines 5-13, the specification describes how to prepare proteorhodopsin mutants:

The present invention provides a method for preparing a proteorhodopsin mutant having improved optical characteristics. The method comprises the steps of:
(a) identifying a conserved amino acid residue of a wild-type proteorhodopsin variant, (b) mutagenizing the conserved amino acid residue and obtaining proteorhodopsin mutants, (c) determining the optical characteristics of the proteorhodopsin mutants, and (d) selecting the proteorhodopsin mutant having improved optical characteristics. The conserved amino acid residue, for example, is a histidine or an arginine residue. The wild-type proteorhodopsin variant can by mutagenized by any method, including but not limited to site-directed mutagenisis, known to a skilled person.

Because (a) the application has identified the conserved histidine amino acid residue in 81 natural proteorhodopsin mutants, (b) proteorhodopsin variants are highly conserved, and (c) the application has described how to prepare proteorhodopsin mutants (e.g. site directed mutageneous) and how to select proper mutants, Applicants respectfully request the Examiner to examine all the amended claims.

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Respectfully submitted,

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